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(71) Applicant: AMERICAN CYANAMID COMPANY
1937 West Main Street P.O. Box 60
Stamford Connecticut 06904-0060(US)

(72) Inventor: Casey, Donald James
9 Revere Place
Ridgefield Connecticut 06877(US)
Inventor: Rosati, Louis
183 Sunrise Hill Road
Norwalk Connecticut 06851(US)
Inventor: Jarrett, Peter Kendrick
24 Chatfield Drive
Trumbull Connecticut 06611(US)

(74) Representative: Wächtershäuser, Günter, Dr.
Tal 29
D-8000 München 2(DE)

(54) Polyesters containing alkylene oxide blocks as drug delivery systems.

(57) The invention is an ABA or AB block copolymer as a well as slow release drug delivery system comprising a drug and the ABA or AB block copolymer wherein one block (B) is a poly (alkylene oxide) and the other blocks (A) are comprised of degradable random copolymers of (1) the cyclic ester of an alpha-hydroxy acid and (2) a second cyclic ester monomer with the proviso that the second cyclic ester monomer is not the same as the first cyclic ester.

EP 0 258 780 A2

## POLYESTERS CONTAINING ALKYLENE OXIDE BLOCKS AND THEIR USE AS DRUG DELIVERY SYSTEMS

Background and Summary of the Invention

The invention relates to diblock and triblock copolymers. The diblock copolymer or AB block polymer has a first block comprising a polyalkylene oxide and a second block consisting essentially of glycolic acid ester and trimethylene carbonate linkages.

The triblock copolymer or ABA block copolymer has a middle block obtained by removing both terminal hydroxyl hydrogéns from either a homopolymer of ethylene oxide, or from a copolymer of ethylene oxide and a cyclic ether. Alternatively, the triblock copolymer has a middle block obtained by removing both terminal hydroxyl hydrogen from a copolymer of a first cyclic ether selected from the group consisting of
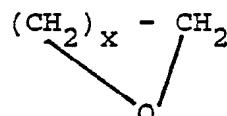
$$(CH_2)_x - CH_2$$
$$\diagdown O \diagup$$

wherein x is 2 to about 9, and a second cyclic ether selected from the group consisting of

$$(CH_2)_y - \overset{R}{\underset{|}{CH}}$$
$$\diagdown O \diagup$$
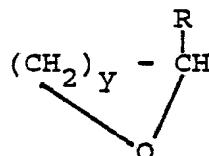
wherein y is 1 to about 9 and R is a C_1 to C_6 alkyl group.

The invention also relates to a slow release drug delivery system comprising a drug, preferably bovine somatotropin (bST) and an ABA or AB block polymer wherein the (B) block is a poly(alkylene oxide) and the blocks (A) are comprised of degradable random copolymers of (1) the cyclic ester of an alpha-hydroxy acid and (2) a second cyclic ester monomer with the proviso that the second cyclic ester monomer is not the same as the first cyclic ester. A preferred polymer is one wherein the first cyclic ester of the alpha-hydroxy acid of the block polymer is glycolide and the second cyclic ester monomer is trimethylene carbonate.

The poly(alkylene oxide) concentration in the block polymer is within the range of about 4 to about 54 weight percent of the block polymer and preferably about 4 to about 30 weight percent and the ratio of glycolide to trimethylene carbonate is within a range of about 45 weight percent glycolide and about 55 weight percent trimethylene carbonate to about 68 weight percent glycolide and about 32 weight percent trimethylene carbonate. The average molecular weight of the B component, poly(alkylene oxide), is with in a range of about 5000 to about 20,000.

Description of the Invention

The AB block polymer is a first block copolymer comprising a polyalkylene oxide and a second block consisting essentially of glycolic acid ester and trimethylene carbonate linkages. In one embodiment, the polyalkylene oxide block is from 5 to 25 percent by weight of the copolymer. In another embodiment, the number average molecular weight of the polyalkylene oxide block is from about 4,000 to 30,000. In yet another embodiment, the polyalkylene oxide block is derived from a polyalkylene oxide terminated on one end by a C_1 to C_6 alkyl group and on the other end by a hydroxyl group.

In a specific embodiment of any of the above embodiments, the polyalkylene oxide block is derived from a homopolymer of ethylene oxide. In another specific embodiment of any of the above, the polyalkylene oxide block is derived from a block or random copolymer of ethylene oxide and a cyclic ether. In a more specific embodiment, the cyclic ether is selected from the group consisting of

$$(CH_2)_x - CH_2$$
$$\diagdown \diagup$$
$$O$$

or

$$(CH_2)_y - \overset{\overset{\textstyle R}{|}}{CH}$$
$$\diagdown \diagup$$
$$O$$
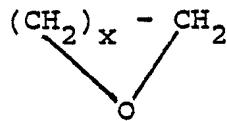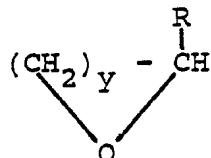
wherein x is 2 to about 9, y is 1 to about 9 and R is a C_1 to C_6 alkyl group.

In yet another specific embodiment, the polyalkylene oxide block is derived from a block or random copolymer of a first cyclic ether selected from the group consisting of

$$(CH_2)_x - CH_2$$
$$\diagdown \diagup$$
$$O$$

wherein x is 2 to about 9, and a second cyclic ether selected from the group consisting of

$$(CH_2)_y - \overset{\overset{\textstyle R}{|}}{CH}$$
$$\diagdown \diagup$$
$$O$$
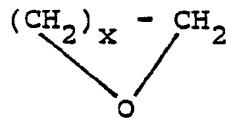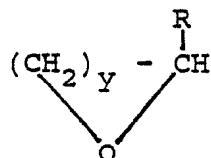
wherein y is 1 to about 9 and R is a C_1 to C_6 alkyl group.

In a more specific embodiment (to the above specific embodiments), a bioabsorbable diblock copolymer has been invented. The inherent viscosity of the copolymer, as measured at 30°C for a 0.5% (w/v) solution in chloroform or methylene chloride, is 0.25 to about 1.50 dl/g.

In the triblock copolymer, the middle block is obtained by removing both terminal hydroxyl hydrogens either form a homopolymer of ethylene oxide, or from a block or random copolymer of ethylene oxide and a cyclic ether. In one embodiment, the cyclic ether is selected from the group consisting of

$$(CH_2)_x - CH_2$$
$$\diagdown \diagup$$
$$O$$

or

$$(CH_2)_y - \overset{\overset{\textstyle R}{|}}{CH}$$
$$\diagdown \diagup$$
$$O$$
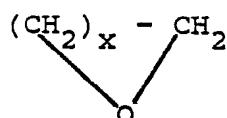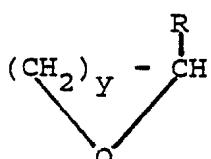
wherein x is 2 to about 9, y is 1 to about 9 and R is a C_1 to C_6 alkyl group.

Further, an alternative triblock copolymer has been invented. The middle block is obtained by removing both terminal hydroxyl hydrogens from a block or random copolymer of a first cyclic ether selected from the group consisting of

$$(CH_2)_x - CH_2$$
$$O$$

wherein x is 2 to about 9, and a second cyclic ether selected from the group consisting of

$$(CH_2)_y - \overset{R}{\underset{}{CH}}$$
$$O$$
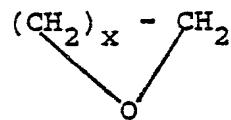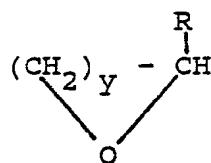
wherein y is 1 to about 9 and R is a C_1 to C_6 alkyl group.

In a further embodiment of any of the above embodiments, each end block of the triblock copolymer consists essentially of glycolic acid esters and trimethylene carbonate linkages. In a specific embodiment, the middle block is from 5 to 25 percent by weight of the copolymer. In a more specific embodiment, the number average molecular weight of the middle block is from about 4,000 to 30,000.

In a most specific embodiment (to the above specific embodiments), a bioabsorbable triblock copolymer has been invented. The inherent viscosity of the copolymer, as measured at 30°C for a 0.5% (w/v) solution in chloroform or methylene chloride, is 0.25 to about 1.50 dl/g.

In an aqueous environment, the thermoplastic hydrogels consisting of ABA or AB block polymers will swell to a predetermined equilibrium value and will release a wide variety of low and high molecular weight (>1000) biologically active materials. In addition, the materials are capable of being completely degraded and eliminated from the body over a period of time. A particular advantage of these materials is their thermoplastic nature; that is, they can be processed by conventional solution or thermal techniques.

Recently, there has been interest in using hydrogels in a wide variety of biomedical (including veterinary) applications such as contact lenses, burn dressings, blood and tissue compatible implants, and drug delivery devices. In the area of controlled drug delivery devices, cross-linked hydrogel materials have met with great success. However, these materials suffer drawbacks, such as a lack of processibility, which are a consequence of their cross-linked nature.

Our approach to this problem was to investigate the use of ABA and AB block copolymers as thermoplastic degradable hydrogels. In these block polymers, the (B) block is a water soluble polymer such as a poly(alkylene oxide) and the blocks (A) are comprised of degradable random copolymers of glycolide (Gly) and trimethylene carbonate (TMC). The middle and end blocks of the block copolymer are chemically incompatible and the result is a phase separated system with crystalline alkylene oxide regions dispersed throughout the Gly/TMC matrix. When exposed to an aqueous environment, the block copolymer segments pick up an amount of water which is a function of the composition and molecular weight of the various block structures. In addition, the low glass transition temperature of the random Gly/TMC blocks allows for facile deformation of the matrix to occur on swelling. This is necessary to accommodate the dimensional changes brought about by the swelling process. The poly(alkylene oxides are poly(C_2-C_4) oxides. Typically, the polyalkylene oxides used as B blocks include hydroxyl ended polyethylene oxide, hydroxyl ended polyethylene oxide-co-propylene oxide, and the monomethyl ether of the hydroxyl ended polyethylene oxide.

Slow release drug delivery systems of the invention may be used as implants or parenteral suspensions prepared from pharmaceutically and pharmacologically acceptable liquid vehicle.

Polymerization Method

The method of choice for preparing the above block copolymers including the ABA triblock copolymers is the melt phase ring-opening copolymerization of glycolide and trimethylene carbonate using specially purified, commercially available difunctional poly(ethylene glycols) as initiators. These polymerizations are conducted in a stirred reactor at 165°C under nitrogen. When maximum melt viscosity has been reached, the polymer is discharged and allowed to cool to room temperature. The polymers can be purified by reprecipitation for methylene chloride solutions into methanol or ethanol.

Determination of Water Uptake

Samples of the above polymers are extruded at 60°-100°C on an extruder to yield fibers of 1,5 mm average diameter. The fibers are then cut into ~1" lengths and several are placed in deionized water at room temperature. At various time intervals, the fibers are withdrawn, wiped thoroughly to remove any surface liquid, and the water uptake is measured gravimetrically. Alternatively, the uptake can be measured with thin films (0.6 mm) prepared by compression molding the polymer at 90°C, or by casting thin films of the polymer from solution.

Fabrication Methods

A. Solution Casting

A solution of polymer (20-50% w/v) is prepared in an appropriate low boiling solvent such as methylene chloride. A biologically active material that is insoluble in methylene chloride, such as bovine somatotropin (bST), is added with rapid stirring to form a viscous slurry. The proportions are chosen so that the active material is 1-75% of the weight of the final dry device. The slurry is then poured into a mold which has been pre-cooled to -78°C. After approximately 15 minutes, the frozen slab is placed in a freezer for 3-4 days to allow most of the solvent to evaporate. Final drying of the solution cast disk is accomplished in a vacuum oven at room temperature. The disk can be cut into squares or, in the preferred method, cryogenically ground through a 20 mesh screen to give particles which are capable of being injected or implanted.

B. Coextrusion

The above polymers and a biologically active material are coextruded at 60-115°C on a laboratory scale extruder. The ratio of active material is chosen to be 1-50% w/w but is preferably 25-50% w/w. The 1.5 mm diameter fibers can be cut into lengths or cryogenically ground through a 20 mesh screen to give particles which are capable of being injected, or the fiber can be directly implanted.

In Vitro Release Measurements

A sample (0.5-2.5 g) of polymer which had been loaded with a biologically active material such as bST is placed into a polypropylene dissolution tube. To simulate physiological conditions, 30 ml of phosphate buffered saline at pH = 7.4 is added and the tube is capped. The dissolution tube is then rotated at 3-7 rpm in a water bath at 37°C. Periodically, an aliquot of solution is removed and replaced by fresh buffered saline. The aliquot is then analyzed for total protein content by using a biuret assay. The protein copper complex is measured spectrophotometrically at 540 nm and is compared to a calibration curve constructed with known amounts of an identical protein. In the preferred method, the entire buffer solution is decanted daily from the dissolution tube and replaced by 30 ml of fresh buffer solution. An aliquot of the decanted buffer solution is then analyzed by the biuret assay method as above.

In Vivo Release Measurements

Polymer which contains bST is ground through a 20 mesh screen and suspended in soybean oil. Six hypophysectomized (hypox) rats are injected with the polymer containing the bST. The amount injected is adjusted so that each animal receives 800 ug of bST. In addition, there are two control groups of six hypox rats. The first group (positive control) each receives 80 ug of bST in buffer daily for 10 days (800 ug total). The second control group receives daily injections of aqueous buffer (negative control). The average weight gains of the 3 groups are then measured over a 10-day period.

The above embodiments are more fully described in the following examples.

Example 1

Purification of Materials

DL-lactide: DL-lactide was purchased from Purac, Inc. One kilogram of DL-lactide is refluxed for I 1/2 hours with toluene (1500 g) which has been dried by distillation from benzophenone ketyl. The residual water is removed from the DL-lactide by collection of the toluene/water azeotrope in a Dean-Stark trap. The dry DL-lactide solution is allowed to cool to room temperature and placed in the refrigerator overnight. The crystallized DL-lactide is then quickly filtered and dried in a vacuum oven at room temperature. Recrystallization yield is 84%.

Polyethylene Glycol-8,000: Polyethylene glycol-8,000 (PEG 8,000) (160 g) is dissolved in methanol (1600ml). The PEG solution is then freed of catalyst impurities and deionized by slowly passing the solution through a methanol conditioned indicating mixed bed anionic and cationic ion-exchange resin (Amberlite MB-3, Rohm and Haas Company, PA, U.S.A.). After elution from the column, the PEG is crystallized by placing the solution in a freezer overnight. The crystalline PEG is then filtered and air dried for 2 hours. The PEG is further purified by recrystallization from acetone (1600 ml). The recrystallized PEG is filtered and dried in a vacuum oven at room temperature overnight. Prior to polymerization, the desired amount of purified PEG is dried further by heating in a vacuum oven at 70°C with P_2O_5 as a desiccant. PEG-14,000 and PEG-20,000 are purified in the same way.

Pluronic F68: Pluronic F68 was purified by the same technique as described for PEG above but without the acetone recrystallization step. The methanol recrystallized Pluronic F68 was filtered and dried in a vacuum oven at room temperature. Prior to polymerization, the Pluronic F68 was further dried by heating in a vacuum oven at 70°C with P_2O_5 as a desiccant.

Pluronic P105: Pluronic P105 was purified by the same method described for PEG above. The polymer was recovered from the methanol solution using a rotary evaporator. Residual methanol was removed by drying in vacuum to constant weight. The material was not recrystallized from acetone. Prior to polymerization the Pluronic P105 was dried further by heating in a vacuum oven at 50°C with P_2O_5 as a desiccant.

Polyethylene Glycol Methyl Ether: Polyethylene glycol methyl ether, nominal molecular weight 5000, was purified in the same way as described for PEG above.

Example 2

Synthesis of (Gly/TMC)-(PEO 14,000)-(Gly/TMC) ABA Triblock Copolymer (Gly/PEO/TMC: 34/41/25)

A 250 ml flask is charged with PEG-14000 (50 g, 0.0036 mole). The flask is placed in a vacuum oven and the PEG is dried overnight under vacuum at 70°C with P_2O_5 as a drying agent. The flask is then placed in a glove bag under N_2. Glycolide (25.0 g, 0.21 mole) and trimethylene carbonate (25.0 g, 0.24 mole) are charged to the flask and the contents are melted and mixed under N_2. The monomer mixture is then quickly transferred into a stirred reactor which has been heated under a nitrogen flow at 165°C. Stannous octoate (0.16 ml, 4.9×10^{-4} mole) is then quickly charged to the reactor with the use of a syringe. The polymer melt is stirred at 40 rpm for approximately 3 hours at 165°C. This time period corresponds to a maximum in the melt viscosity. The polymer is discharged from the reactor and allowed to cool to room temperature. A portion of the crude polymer (42.8 g) is dissolved in CH_2Cl_2 (250 ml) and reprecipitated dropwise into

rapidly stirred absolute ethanol (3000 ml). After filtration and drying to constant weight, the reprecipitation yield was determined to be 96%. The inherent viscosity of the polymer (0.5%, in CHCl$_3$ at 30°C was 0.38 dL/g. The composition was analyzed by ^{1}H-NMR and was found to be 34/41/25 weight percent Gly/PEO/TMC. The Tg of the polymer was 11°C, the melting point (Tm) was 59°C.

Examples 3-14

Several polymers were prepared as in Example 2 with varying PEG contents and PEG molecular weights (Table I). In many of the Gly/PEO/TMC triblock copolymers, the charged ratio of Gly/TMC is 60/40 weight percent. This allows for maximum Tg of the rubbery end blocks (9°C) while still maintaining solubility in common organic solvents. Differential scanning calorimetry (DSC) clearly shows phase separation in these materials. The Tg of the rubbery end blocks (7°-16°C) is very close to the Tg of a 60/40 random Gly/TMC polymer. In addition, the Tm of the crystalline PEO segments are only lowered 5°-10°C.

Example 15

Synthesis of (Gly/TMC)-(PEO-8000)-(Gly/TMC) ABA. (Gly/PEO/TMC) 59/6/35

Glycolide (117.0 g, 1.01 mole), trimethylene carbonate (71.0 g, 0.70 mole), PEG-8000 (12.0 g) and stannous octoate (0.33 ml 1.0 $\times$ 10^{-3} mole) were combined in a stirred reactor as in Example 2. The reaction mixture was then stirred at 169°C and 36-40 rpm for 1.5 hours. The polymer was recovered as in Example 2. The properties of this polymer are summarized in Table I.

Example 16

Synthesis of (Gly/TMC)-(PEO-8000)-Gly/TMC) ABA (Gly/PEO/TMC: 54/8/38)

Glycolide (110.4 g, 0.95 moles), trimethylene carbonate (73.6 g, 0.72 moles), PEG-8000 (16.0 g) and stannous octoate (0.32 ml, 9.96 $\times$ 10^{-4} moles) were combined and allowed to polymerize as in Example 15. The properties of this polymer as summarized in Table I.

Example 17

Synthesis of (Gly/TMC)-(PEO-8000)-Gly/TMC) ABA, (Gly/PEO/TMC: 54/10/36

Glycolide (108.0 g, 0.93 moles), trimethylene carbonate (72.0 g, 0.71 moles), PEG-8000 (20.0 g) and stannous octoate (0.32 ml, 9.96 $\times$ 10^{-4} moles) were combined and allowed to polymerize as in Example 15. The properties of this material are summarized in Table I.

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TABLE I

Glycolide/PEO/TMC Polymers

Ex.	Charged Composition (Gly/PEO/TMC Wgt. %)	PEG MW	η_{inh} (Solvent)		Gly/PEO/TMC Composition by ^{1}H-NMR (wt %)		Tg (°C)	Tm (°C)
			As Polymerized	Reprecipitated	As Polymerized	Reprecipitated		
3	25/50/25	14,000	---	0.40 ($CHCl_3$)	---	30/43/27	---	---
4	32/50/18	14,000	---	0.45 (CH_2Cl_2)	---	31/54/15	---	---
5	48/20/32	14,000	---	0.45 ($CHCl_3$)	---	49/19/32	16	57
6	54/10/36	14,000	---	0.34 (CH_2Cl_2)	---	55/11/34	12	54
7	42/30/28	14,000	0.45 (CH_2Cl_2)	0.45 (CH_2Cl_2)	---	44/29/27	15	58
8	42/30/28	8,000	0.40 (CH_2Cl_2)	0.38 (CH_2Cl_2)	---	43/31/26	16	55
9	48/20/32	8,000	0.42 (CH_2Cl_2)	---	48/21/31	---	14	55
10	54/10/36	8,000	0.46 (CH_2Cl_2)	0.33 ($CHCl_3$)	50/10/40	50/8/42	10	53
11	54/10/36	20,000	---	---	---	---	7	47
12	48/20/32	20,000	---	---	---	---	6	52

TABLE I (Continued)

Glycolide/PEO/TMC Polymers

Ex.	Charged Composition (Gly/PEO/TMC Wgt. %)	PEG MW	ηinh (Solvent)		Gly/PEO/TMC Composition by ^{1}H-NMR(wt %)		Tg (°C)	Tm (°C)
			As Polymerized	Reprecipitated	As Polymerized	Reprecipitated		
13	42/30/28	20,000	--	--	--	----	11	54
14	57/5/38	8,000	0.41 (CHCl$_3$)	0.38 (CHCl$_3$)	57/5/38	58/5/37	--	--
15	58/6/36	8,000	0.42 (CHCl$_3$)	0.40 (CHCl$_3$)	59/6/35	59/6/35	--	--
16	55/8/37	8,000	0.44 (CHCl$_3$)	0.42 (CHCl$_3$)	53/8/39	54/8/38	--	--
17	54/10/36	8,000	0.45 (CHCl$_3$)	0.40 (CHCl$_3$)	54/10/36	54/10/36	--	--

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Example 18

Synthesis of (Gly/dl-Lact)-(PEO-8000)-(Gly/dl-Lact) ABA, (Gly/dl-Lact/PEO: 36/54/10)

Glycolide (54.0 g, 0.46 moles), dl-lactide (81.0 g, 0.56 moles), PEG-8000 (15.0 g) and stannous octoate (0.32ml, 9.96×10^{-4} moles) were combined and allowed to polymerize as in Example 2. The properties of this polymer are summarized in Table II.

Example 19

Synthesis of (Gly/1-Lact)-(PEO-8000)-(Gly/1-Lact) ABA: (Gly/1-Lact/PEO: 27/65/8)

Glycolide (53.2 g, 0.46 moles), 1-lactide (130.8 g, 0.91 moles), pEG-8000 (16.0 g) and stannous octoate (0.05 ml, 1.56×10^{-4} moles) are combined and allowed to polymerize by the procedure described in Example 15. The properties of this polymer are summarized in Table II.

Example 20

Synthesis of (1-Lact/TMC)-(PEO-8000)-(1-Lact/TMC) ABA. (1-Lact/TMC/PEO: 43/49/8)

1-Lactide (88.0 g, 0.61 moles), trimethylene carbonate (96.0 g, 0.94 moles), PEG-8000 (16.0 g) and stannous octoate (0.31 ml, 9.74×10^{-4} moles) are combined and allowed to polymerize by the procedure described in Example 15. The properties of this polymer are summarized in Table II.

Example 21

Synthesis of (Gly/dl-Lact)-(PEO-20,000)(Gly/dl-Lact) ABA,(Glv/dl-Lact/PEO: 21/25/54)

dl-lactide (25.0 g, 0.17 moles), glycolide (25.0 g, 0.21 moles), PEG 20,000 (50.0 g) and stannous octoate (0.16 ml, 4.94×10^{-4} moles) are combined and allowed to polymerize by the procedure described in Example 2. The properties of this polymer are described in Table II.

Table II

Terpolymers With PEO Midblocks and Various Endblocks

Ex.	Charged Composition	PEG MW	ηInh (Solvent)		Composition by ¹H-NMR (Wt%)		Tg	Tm
			As Polymerized	Reprecipitated	As Polymerized	Reprecipitated		
18	Gly/dl-lactide/PEO: 36/54/10	8,000	0.49(CHCl$_3$)	0.35(CHCl$_3$)	36/54/10	36/54/10	--	--
19	Gly/l-lactide/PEO: 27/65/8	8,000	0.73(CHCl$_3$)	----	27/65/8	----	36	--
20	l-Lactide/TMC/PEO: 44/48/8	8,000	0.56(CHCl$_3$)	----	43/49/8	----	0	--
21	Gly/dl-lactide/PEO: 25/25/50	20,000	----	0.43(CHCl$_3$)	----	21/25/54	42	57

Example 22

Swelling Behavior of Examples 3, 4 and 21

A film was prepared by solution casting a 20% w/v solution of the polymer of Example 3 in CH$_2$Cl$_2$. After the solvent had evaporated overnight, the film was dried further under vacuum at room temperature overnight. Films made from the polymers of Example 3, 4 and 21 were placed in water at 37°C with stirring. After 24 hours, films from Example 3 and Example 4 had formed emulsions. By day 3, the film from Example 21 had also formed an emulsion.

Example 23

Swelling Behavior of Example 7 (Gly/PEO/TMC: 44/29/27)

A sample of the polymer from Example 7 (1.5 g) was extruded at 110°C on an extruder to yield a 1.5 mm diameter fiber. From the fiber 5 samples, lengths each approximately 1" were cut. The samples were placed in deionized water at room temperature. Periodically, the samples were withdrawn, wiped dry, and the water uptake measured gravimetrically. The water uptake is shown in Table III. From the values at 1280 min., the equilibrium water uptake for fibers was calculated to be 232 ± 3%.

The same type of water uptake analysis was performed on 4 samples of films of the polymer of Example 7 (12 $\times$ 4 $\times$ 0.6 mm). The results are shown in Table III. The shorter time to reach an equilibrium value of water uptake in the films is attributable to the greater surface-to-volume ratio in the films.

Table III

Water Uptake by Fibers and Films of 44/29/27 Gly/PEO/TMC (Ex. 7)

Fibers		Films	
Time (min)	% H_2O^A Uptake	Time (min)	% H_2O^A Uptake
5	31.1	5	136.7
18	60.9	22	238.7
32	89.3	35	271.0
45	107.9	63	279.5
65	133.6	81	282.2
90	158.2	216	279.1
118	183.7	363	253.5
148	204.3	1560	266.3
179	223.3		
1155	237.6		
1280	235.5		

$$A = \frac{(Wt\ Swollen - Wt\ Dry)}{Wt\ Dry} \times 100$$

Example 24

Swelling of Various Hydrogels

Water uptake experiments were carried out on fibers of several Gly/PEO/TMC hydrogels and one Gly/dl-Lactide/PEO hydrogel (Table IV). Measurements were carried out at room temperature in deionized water. All reported equilibrium uptake values are averages of 4 or 5 samples.

TABLE IV

Combined Swelling Data on Polymers

Example	Polymer	PEG MW	PEO Content (Wgt. %)	% H_2O Uptake	Teg
14	Gly/PEO/TMC	8,000	5	27.9 ± 5.4[1,3]	13 days
10	Gly/PEO/TMC	8,000	8	124.1 ± 7.4[1,3]	1 day
10	Gly/PEO/TMC	8,000	10	11.3 ± 0.9[1,2]	4
18	Gly/dl-lactide/PEO	8,000	10	9.9 ± 1.3[1,3,5]	5
9	Gly/PEO/TMC	8,000	21	163.0 ± 1.8[1,2]	4
8	Gly/PEO/TMC	8,000	31	224.5 ± 15.1[1,2]	4
6	Gly/PEO/TMC	14,000	11	125.8 ± 4.5[1,3]	4
5	Gly/PEO/TMC	14,000	19	164.9 ± 11.2[1,3]	4
7	Gly/PEO/TMC	14,000	29	235.9 ± 3.1[1,3]	17 hrs.
7	Gly/PEO/TMC	14,000	29	260.8 ± 10.3[3,6]	20 min.
11	Gly/PEO/TMC	20,000	10	61.0 ± 0.5[1,2]	4
12	Gly/PEO/TMC	20,000	20	169.0 ± 0.8[1,2]	4
13	Gly/PEO/TMC	20,000	30	289.2 ± 5.6[1,2]	4

1 = fiber (dimensions = 10 mm x 1.5 mm diameter)
2 = as polymerized
3 = reprecipitated
4 = not determined
5 = not at equilibrium by day 13
6 = film (dimensions = 12 x 4 x 0.6 mm)

Several generalizations about the data in Table IV can be made. The time to reach an equilibrium value of water uptake depends on the shape of the sample (Example 7 fiber vs. film). It would also appear that the time to reach an equilibrium value of water uptake decreases as the PEO content increases.

Within the scatter in the data, equilibrium water uptake is linearly related to the PEO content in the range 5-30%. There is no noticeable effect of the MW of the PEO block on the swelling of these triblock polymers (within the range of PEO MW 8,000-20,000).

One important difference noted in Table IV is the contrast of Example 10 (Gly/PEO/TMC) with Example 18 (Gly/PEO/dl-Lactide). Both have approximately the same percent of PEO 8,000; however, a re-precipitated sample of Example 10 had an equilibrium water content of 124% (Teg 1 day) vs. 9.9% by day 13 for a reprecipitated sample of Example 18. The difference can be rationalized by looking at the differences of the two matrices. In the case of the sample of Example 10 the rubbery Gly/TMC matrix is free to deform to accommodate the dimensional changes caused by the swelling. In Example 18 however the Gly/dl-Lactide matrix is in a glassy state. This should result in a slower water uptake curve (note that at 13 days equilibrium has not been reached) until the Gly/dl-Lactide matrix is sufficiently plasticized by water.

Example 25

Synthesis of (Gly/TMC) [Pluronic F68] (Gly/TMC) ABA (Gly/Pluronic F68/TMC: 56/8/36) Multiblock Copolymer

Pluronic F68 (BASF Wyandotte, USA) is a triblock copolymer of poly(ethylene oxide) (PEO) (80 mole %) and poly(propylene oxide) (PPO) (20 mole %) where PPO forms the middle block and the total molecular weight is about 8400. Like PEO, this copolymer is terminated with hydroxyl groups which can be used as an initiator for the ring opening polymerization of cyclic esters.

Glycolide (82.8 g), trimethylene carbonate (55.2 g) Pluronic F68 (12.0 g) and stannous octoate (0.242 ml), where combined in a stirred reactor as in Example 2. The reaction mixture was then stirred at 165°C and 40 rpm for 1.5 hours. The polymer was recovered as in Example 2 and then characterized as follows:
ηlnh (CHCl₃):0.40; Composition: 56/8/36 (¹H-NMR); Tg:14°C; Tm 42°C.

Example 26

Synthesis of (Gly/TMC) [Pluronic P105] (Gly/TMC) ABA (Gly/Pluronic P105/TMC: 56/9/35) Multiblock Copolymer

Pluronic P105 (BASF Wyandotte, USA) is triblock copolymer of poly(ethylene oxide) (PEO) (50 mole %) and poly(propylene oxide) (PPO) (50 mole %) where PPO forms the middle block and the total molecular weight is about 6500. Like PEO, this copolymer is terminated with hydroxyl groups which can be used as an initiator for the ring opening polymerization of cyclic esters.

Glycolide (54 g), trimethylene carbonate (36 g) Pluronic F68 (10.0 g) and stannous octoate (0.19 ml), where combined in a stirred reactor as in Example 2. The reaction mixture was then stirred at 165°C and 40 rpm for 1.5 hours. The polymer was recovered as in Example 2 and then characterized as follows:
ηlnh (CHCl₃):0.35; Composition: 56/9/35 (¹H-NMR).

Example 27

Synthesis of (PEO)-(Gly/TMC) AB (Gly/PEO/TMC: 57/6/37) Diblock Copolymer

Poly(ethylene glycol) methyl ether (PEO-5000) was purchased from Aldrich Chemical Company. The molecular weight was reported to be 5000. This polymer is terminated by one hydroxyl group and one methyl ether group. Only one end of this molecule, therefore, can be used to initiate the ring opening polymerization of cyclic esters, forming an AB diblock copolymer.

Glycolide (84.6 g), trimethylene carbonate (54.4 g) PEO 5000 (10.0 g) and stannous octoate (0.242 ml), where combined in a stirred reactor as in Example 2. The reaction mixture was then stirred at 165°C and 40 rpm for 1.5 hours. The polymer was recovered as in Example 2 and then characterized as follows:
ηinh (CHCl₃):0.42; Composition: 57/6/37. (¹H-NMR); Tg:12°C Tm:59°C.

Example 28

In Vitro Release of Theophylline (30% w/w loaded hydrogel)

Theophylline and hydrogel Example 10 [Gly/PEO 8,000/TMC (50/8/42] were mixed and extruded at 80°C on a laboratory scale extruder. The loading of theophylline was 30% w/w. To a 2,000 ml 24/40 erlemeyer flask, 0.2939 g of the hydrogel formulation. 882 ml of phosphate buffer (pH 6.89) and a magnetic stirring bar were charged. The flask was quickly placed into a 39°C water bath and stirred was started with the use of a submersible water driven stir plate. A peristaltic pump was used to circulate the buffer solution through a flow-through UV cell and theophylline release was monitored by following the absorbance in the region 284-287 nm. The fractional release for the 30% loaded hydrogel Example 10 is given in Table V. The release curve is typical of release from a metrix type device. Release from this type of device would be expected to follow a $t^{1/2}$ dependence (linear with square root of time) on the release rate. When plotted versus the square root of time, release is linear up to 85-90% of the total fractional release.

TABLE V

Theophylline Release from 30% Loaded Hydrogel Example 10

Time (min)	Percent Released
8	9.3
13	18.7
18	24.0
23	30.7
30	36.0
36	40.0
51	52.0
66	61.3
81	68.0
96	73.3
111	77.3
141	84.0
186	89.3
249	93.3
429	97.3
819	98.7
1149	100.0

Examples 29-31

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Theophylline Release from 2010 and 5% Loaded Hydrogel of Example 10

Release of theophylline from hydrogel of Example 10 at 20%, 10% and 5% w/w loadings was carried out in the same manner as in Example 28. For this system, the release rates were very similar for loadings in the range of 5-20% with 100% of the theophylline released over a 13-l5 hour period.

Example 32

Theophylline Release from 5% Loaded Hydrogel of Examole 14

Release of theophylline from 5% loaded hydrogel Example 14 (Gly/PEO 8,000/TMC 58/5/37) showed a much lower release rate as compared to hydrogel Example 10 (Table VI). This is attributable to the differences in swelling behavior of the two polymers. Hydrogel Example 10 (due to its higher PEO content) reaches an equilibrium water content of 124% in 24 hours. On the other hand, hydrogel Example 14 with only 5% PEO picks up approximately 28% water in a 13 day period.

TABLE VI
Theophylline Release from 5% Loaded Hydrogel Example 14

Time (hrs)	Percent Released
0.5	2.0
1.12	2.3
4.65	2.4
7.6	2.6
10.6	3.4
25.15	6.7
46.15	7.3
63.15	7.9
82.15	8.2

Examples 33-44

In Vitro Release of bST at 37°C, pH = 7.4

In vitro release of bST was measured for a number of hydrogel compositions (Table VII) and fabrication methods. The results indicate that, in general, bST release rates increase as the PEO content of the hydrogel increases. As previously discussed, higher PEO content leads to increased equilibrium water uptake which should allow for faster bST diffusion through the swollen gel. Several other trends are apparent from the results in Table VII. The fabrication method greatly influences the release rates of bST from the hydrogels. In general, it was found that extruded fibers gave lower release rates than solution cast films. The cast films contained a large number of voids and often delaminated due to the drying process. This gave a formulation with a much higher surface to volume ratio as compared to the extruded fibers. This high surface/volume ratio accounts for the high release after only 1 day for the solution cast films.

No discernible differences in release rates as a function of PEO mw could be detected. Again, this is expected as it previously has been shown that, in the mw range studied, PEG mw did not influence the swelling behavior of the hydrogels. Finally, it has been demonstrated that release rates can be modified by blending various additives into the formulations. A blend of bST/hydrogel (Example 10) and a Gly/L-lactide

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(40/60) polymer ηinh = 0.50 (25/50/25) was extruded. The measured in vitro release rate of the blend was approximately 2/3 of the release rate for the hydrogel. By blending in a non-swelling Gly/L-lactide polymer, it serves to lower the overall PEO content and reduce the water uptake of the hydrogel. The measured release rates can also be increased by blending in a water soluble filler. When sorbitol was added to the previously described blend, the measured release rates were greater than the parent hydrogel release rates. The water soluble filler is leached out into the dissolution media leaving a more porous matrix which facilitates the release of the active material.

0 258 780

TABLE VII

In Vitro Release of bST

$37^{\circ}C$, pH 7.4

Example No.	Polymer Example	PEG MW	PEG Content (wt %)	bST Loading	Fabrication Method[C]	Day 1	2	3	4	5	6
33	10	8,000	8	25	SC	76.9	78.5	---	---	---	79.1
34	10	8,000	8	25	EX	22.1	30.2	---	---	31.2	32.7
35	10	8,000	8	25[A]	EX	14.4	17.1	---	---	20.2	20.2
36	10	8,000	8	25[B]	EX	38.0	41.9	---	---	---	36.9
37	9	8,000	21	25	SC	75.6	78.8	---	---	---	77.8
38	8	8,000	31	25	SC	76.0	88.2	77.4	---	---	89.2
39	6	14,000	11	25	SC	60.2	67.4	66.4	---	---	77.9
40	5	14,000	19	25	SC	75.0	76.6	---	---	---	79.0
41	7	14,000	29	25	SC	84.0	84.7	---	---	---	86.7
42	11	20,000	10	25	EX	---	37.6	---	---	58.6	---
43	12	20,000	20	25	EX	61.9	78.9	---	---	78.8	---
44	13	20,000	30	25	EX	39.6	61.2	---	---	85.5	---

A = Formulation is a blend (25% bST/50% Ex. 10/25% Gly/L-lact ηinh=0.50

B = Formulation is a blend (25% bST/25% Ex. 10/25% sorbitol/25% Gly/L-lact ηinh=0.50

C = EX = extruded

SC = solution cast

Example 45

In Vitro Release of bST at 37°C, pH = 9.4

Accelerated in-vitro release of bST was measured from fibers of the polymer Example 26. Polymer plus bST (40% loading) were extruded as in Example 33. It was found that this formulation released bST continuously over at least a 22 hour period at pH 9.4 and 37°C.

Example 46

In-vitro Release of bST at 37°C, pH = 9.4

Accelerated in-vitro release of bST was measured from fibers of the polymer of Example 27. Polymer plus bST (40% loading) were extruded as in Example 33. It was found that this formulation released bST continuously over at least a 22 hour period at pH 9.4 and 37°C.

Examples 47-48

In Vivo Release of bST in Hypox Rats

Based on the in vitro release curves, two formulations were tested for in vivo release of bST in hypox rats. The experimental details of the in vivo measurements were discussed previously. The results are shown in Table VIII. Both formulations show growth in hypox rats throughout the 10 day test period.

TABLE VIII

In Vivo Release Data

25% bST Loaded Ground Matrices

Ex. No.	% PEO	PEO MW	Weight Gain (grams)		
			0-3 Days	0-7 Days	0-10 Days
47	10	8,000	5.6 ± 1.0	10.0 ± 1.4	12.3 ± 1.5
48	A	A	8.8 ± 0.86	13.8 ± 1.9	15.6 ± 2.0
Control[B]			8.6 ± 1.3	15.8 ± 1.3	25.5 ± 1.7

A = Blend 33% [Example 10]

        67% [(Gly/lact) 40/60 η_{inh} = 0.50]

B = 10 injections (80 µg/day)

Claims

1. A diblock copolymer having a first block comprising a polyalkylene oxide and a second block consisting essentially of glycolic acid ester and trimethylene carbonate linkages.

2. A diblock copolymer of Claim 1 wherein the polyalkylene oxide block is from 5 to 25 percent by weight of the copolymer.

3. A diblock copolymer of Claim 1 or 2 wherein the number average molecular weight of the polyalkylene oxide block is from about 4,000 to 30,000.

4. A diblock copolymer of Claim 4 wherein the polyalkylene oxide block is derived from a block or random copolymer of a first cyclic ether selected from the group consisting of

$$(CH_2)_x - CH_2$$
$$\diagdown O \diagup$$

wherein x is 2 to about 9, and a second cyclic ether selected from the group consisting of

$$(CH_2)_y - \overset{\overset{R}{|}}{CH}$$
$$\diagdown O \diagup$$
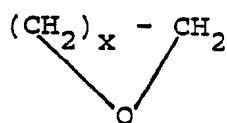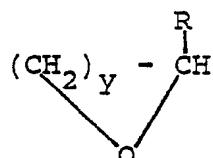
wherein y is 1 to about 9 and R is a C_1 to C_6 alkyl group.

5. A triblock copolymer useful in non-fiber form having a middle block obtained by removing both terminal hydroxyl hydrogens from either a homopolymer of ethylene oxide, or from a block or random copolymer of ethylene oxide and a cyclic ether.

6. A slow release drug delivery system comprising

a drug and

an ABA or AB block polymer wherein the (B) block is a poly(alkylene oxide) and the blocks (A) are comprised of degradable random copolymers of (1) the cyclic ester of an alpha-hydroxy acid and (2) a second cyclic ester monomer with the proviso that the second cyclic ester monomer is not the same as the first cyclic ester.

7. A drug delivery system according to Claim 6 wherein the polymer is a ABA block polymer, and the first cyclic ester is glycolide and the second cyclic ester monomer is trimethylene carbonate.

8. A drug deliver system according to Claim 7 wherein the B block is polyethylene oxide or polyethylene oxide-co-propylene oxide.

9. A drug delivery system according to Claim 7 wherein the drug is bovine somatotropin or theophylline and the poly(ethylene oxide) comprises from about 4 to about 54 weight % of the ABA polymer and the average molecular weight of the poly(ethylene oxide) is within a range of 6,000-25,000.

10. A drug delivery system according to Claim 6 wherein the polymer is an AB block polymer and the first cyclic ester is glycolide and the second cyclic ester monomer is trimethylene carbonate.